REMARKS

The Office Action of September 12, 2000 presents the examination of claims 2-10, 12, and 13. No new matter is inserted into the application. Applicants also wish to extend appreciation to the Examiner for the productive Interview conducted on January 3, 2001.

Sequence Rules Compliance

Enclosed herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a Sequence Listing to be inserted into the specification as indicated above. The Sequence Listing in no way introduces new matter into the specification.

Also submitted herewith in full compliance with 37 C.F.R. §§1.821-1.825 is a computer readable form of the Sequence Listing. The computer readable form of the Sequence Listing, file "0171-0613P.ST25.txt", is identical to the paper copy, except that it lacks formatting.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner rejects claims 2-10, 12, and 13 under 35 U.S.C. § 112, first paragraph. This is an enablement rejection. Applicants respectfully traverse. Reconsideration of the claims and withdrawal of the instant rejection are requested.

Specifically, the Examiner asserts that the specification does not describe the present invention in enough detail that one skilled in the art could carry out the invention. Applicants respectfully disagree.

The Examiner asserts there is no support for the relationship between A/B and B/A in the specification. Further, in the Interview Summary dated January 3, 2001, the Examiner writes

> Agreement was reached that the specification needs to provide antecedent support for the mathematical formulas recited in the claims. Mr. Sisson noted that while original claim 2 provides literal support for such formulas now found in claim 13, he could not locate support for such in the body of the specification.

Applicants make clear that the amount of target DNA is "A", and the total amount of sample DNA is "B". The total amount of sample DNA consists of target DNA plus wild-type DNA. *Thus, A/B is the fractional equivalent of the amount of target DNA content in the total sample DNA.* The meaning of A/B in claim 13 is supported by the specification, page 10 (line 31) to page 13 (line 33), and also Example 1 beginning on page 23, and is explained further below.

As shown in the calculations of Table 1 and Figure 2, when the ratio of the labeled standard DNA to the sample DNA is 1:20, and the content of target DNA (which has the base sequence the same as the labeled standard DNA) is 5%, then the index value is

50 (as shown in Table 1). Conversely, when the ratio of the labeled standard DNA to the sample DNA is 1:160, and the content of target DNA (having the base sequence the same as the labeled standard DNA) is 1%, then the index value is less than 50.

These examples show that the target DNA can be detected and identified by *increasing the excessiveness* of the sample DNA in relation to the labeled standard DNA. As shown above, when the target DNA amount is higher (i.e. 5%), then the amount of sample DNA is 20 times that of the labeled standard DNA. On the other hand, when the amount of target DNA is lower (i.e. 1%), then the amount of sample DNA is increased to 160 times that of the labeled standard DNA. Thus, when the amount of sample DNA is increased to excessiveness over the amount of labeled standard DNA, smaller amounts of target DNA may be identified in the sample. This process works even when the amount of target DNA is low. As such, the present invention provides a process for competitive hybridization to occur even when the amount of target DNA is low, because the labeled standard DNA can be theoretically calculated from the excessiveness and the obtained index value.

Example 1 shows two systems using the labeled standard DNA and the sample DNA mixed at particular ratios. In one system, the labeled standard DNA and the sample DNA are mixed at a ratio of 1:20. Note that the labeled standard DNA and sample DNA are

quantified as known in the art. In the second system, the labeled standard DNA and the sample DNA are mixed at a ratio of 1:40. Competitive hybridization then occurs. The results are shown in Figure 3. In Figure 3, the x axis represents the index value, and the y axis represents the percentage of target DNA in the sample DNA.

When the labeled standard DNA and the sample DNA are mixed at a ratio of 1:20, an index value of 50 is obtained at the mutant DNA percentage 5.0% (see Figure 3). At this percentage, the mutant DNA is sufficiently detectable. In other words, the mutant DNA content of about 5% corresponds with the A/B (1/20=0.05=5.0%). Again, A/B is the fractional equivalent of the amount of target DNA in the sample DNA. Conversely, B/A is the excessiveness of the sample DNA to the labeled standard DNA (which has the same sequence as the target DNA). In this case, B/A=20/1.

Next, the mixing ratio of 1:40 is explained. When the labeled standard DNA and the sample DNA are mixed at a ratio of 1:40, an index value of about 50 is obtained when the mutant DNA content is about 2.5% (see Fig. 3). This corresponds to the value of A/B (1/40=0.025=2.5%). Further, the excessiveness of the sample DNA is 40 times that of the labeled standard DNA (B/A=40/1). The target DNA is sufficiently detectable at this percentage.

The present invention provides an assay that is capable of reliably detecting, identifying, and quantifying target DNA (having a base sequence the same as the labeled standard DNA) present in a sample DNA, *even if the content of the target DNA is minute*. The following steps enable such an assay of high precision:

1. preliminarily selecting the detection limit for the target DNA present in the sample DNA;
2. determining the excessiveness of the sample DNA to be added to the labeled standard DNA depending on the selected detection limit; and
3. adding the sample DNA to adequate excessiveness to the labeled standard DNA to promote competitive hybridization.

As the above steps illustrate, it is important to use the concept of A/B in the present invention in order to determine the excessiveness of the sample DNA by using the concept of B/A.

Applicants respectfully submit that the above discussion of the present invention fully clarifies to the Examiner that the present invention is indeed enabled by the instant specification. Applicants further submit that all other issues raised by the Examiner in the Office Action of September 12, 2000 are rendered moot by either the above response or the Interview of January 3, 2001. For these reasons, Applicants

respectfully request that the rejection under 35 U.S.C. § 112, first paragraph be withdrawn.

Remaining Issues from Interview

Also in the Interview summary dated January 3, 2000, the Examiner writes,

> Mr. Sisson expressed concern over how the claimed method appeared to be a combination of polymerase chain reaction and competitive hybridization reaction. Agreement was reached in that both of these methods were known in the art at the time of filing. Mr. Sisson directed attention to applicant's PCT publication WO 95/02068 which seemed to suggest the claimed invention.

Applicants note that a rejection over prior art has not been made. However, Applicants address the Examiner's remarks by providing the following comments.

In the present invention, the concept of B/A is used to add an excessive amount of sample DNA to the labeled standard DNA for competitive hybridization. The label intensity of the hybridizate is then measured. In other words, the detection is conducted at an optimal sensitivity level corresponding to the content of the target DNA, allowing a significant change in the measured label intensity even with small amounts of target DNA.

By contrast, in the method of WO 95/02068, an excessive amount of *non-labeled standard DNA* is added to *labeled sample DNA* to allow for competitive hybridization. Thus, the method of

WO 95/02068 is different in at least two ways: (1) the DNA that is labeled in the present invention is the standard DNA, whereas the DNA that is labeled in WO 95/02068 is the sample DNA, and (2) the DNA added in an excessive amount in the present invention is the sample DNA, whereas the non-labeled standard DNA is added in an excessive amount in WO 95/02068. Thus, WO 95/02068 cannot anticipate the present invention.

Furthermore, the present invention is not obvious over WO 95/02068. The method of WO 95/02068 fails to disclose or suggest the concept of A/B. As stated earlier, the concept of A/B is the fractional equivalent of the percentage of target DNA in a sample DNA, and is important for determining the excessiveness of the sample DNA by using the concept of B/A. Further, the label intensity of the hybridizate exhibits a significant change, even when the content of the target DNA is small. The method of WO 95/02068 fails to provide or suggest a such a concept and therefore does not obviate the present invention.

In summary, Applicants submit that all of the present claims define patentable subject matter such that this application should be placed into condition for allowance. Early and favorable action of the merits of the present application is thereby respectfully requested.

If the above amendments for some reason do not place the present application into a condition for allowance, the Examiner is respectfully requested to contact Kristi L. Rupert, Ph.D. (Reg. No. 45,702) at 703-205-8000 to arrange for a personal interview in order to expedite prosecution of the present application.

Pursuant to 37 C.F.R. §§ 1.17 and 1.136(a), Applicant(s) respectfully petition(s) for a two (2) month extension of time for filing a reply in connection with the present application, and the required fee of $$380.00 is attached hereto.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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